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Session H. Lung cancer

H34 KRAS has a role in acquired resistance to EGFR-TKIs in NSCLC: an analysis on circulating tumor DNA

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Background: Activating mutations of *KRAS* oncogene drive resistance to EGFR inhibition by providing an alternative signal transduction pathway [1]. In non-small cell lung cancer (NSCLC), the efficacy of treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs) depends on activating *EGFR* mutations that are mutually exclusive with *KRAS* mutations. However, pharmacological inhibition of *EGFR* signaling has the potential to select cells whose growth may depend, at least in part, on alternative proliferation pathways or continued EGFR signaling due to the c.2369C > T (p.T790M) gatekeeper mutation within the ATP-binding pocket of EGFR. NSCLC heterogeneity can drive the therapeutic decisions; therefore, tissue availability is increasingly recognized as a crucial issue [2]. Unfortunately, the location of the tumor and the risk of complications are serious limitations to re-biopsies in NSCLC. Alternatively, the detection of somatic mutations in cell-free tumor DNA (cftDNA) released in plasma could be instrumental for a better understanding of the genetic modifications driven by the selective pressure of drug treatments on NSCLC [3].

Material and methods: This study used cell-free circulating tumor DNA (cftDNA) to evaluate the appearance of codon 12 *KRAS* and p.T790M *EGFR* mutations in 33 advanced NSCLC patients that progressed after an EGFR-TKI. Six ml of blood samples were drawn from patients at disease progression and cftDNA was extracted by Circulating Nucleic Acid extraction kit (Qiagen) and analysed by digital droplet PCR (BioRad).

Results: *KRAS* mutation at codon 12 alone or in combination with p.T790M was demonstrated in 3 (9.1%) and 13 patients (39.4%), respectively. p.T790M was detected in 11 subjects (33.3%) alone and in 13 patients (39.4%) with mutant KRAS. Six patients (18.2%) were negative for both *KRAS* and p.T790M. In 8 subjects paired tumor re-biopsy/plasma samples were available; the percent concordance of tissue/plasma was 62,5% for p.T790M and 37,5% for *KRAS*.

Conclusions: In conclusion, mutation of *KRAS* could be an additional mechanism of escape to EGFR-TKI and cftDNA is a feasible approach to monitor the molecular development of drug resistance. Therefore, the clinical relevance of this finding, expecially for what concerns *"mut"KRAS*, needs to be evaluated prospectively.

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